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CHI

Persistent

Transient

Diazoxide responsive

Diazoxide unresponsive

Persistent
Histological subtypes

**Diffuse disease**

Histological abnormalities in beta cells throughout the pancreas

**Focal disease**

Focal islet-cell hyperplasia within the lesion, rest of the pancreas normal
18F-DOPA-PET/CT
Focal lesion in head of pancreas junction of portal vein and SMV (6.1mm)

Outline of pancreas

18-F-DOPA PET/CT Scan
Focal lesion at tip of pancreas, junction of spleen and left kidney (5.1mm)
Laparoscopic Surgery

Focal lesion
Diffuse disease
Surgery

• Severe diffuse CHI – unresponsive to diazoxide/octreotide

• 95% to 98% pancreatectomy

• Post op complications – ongoing hypoglycaemia, diabetes mellitus, exocrine pancreatic insufficiency
Surgery - Outcomes

• 105 children (58 diffuse)
• Diffuse - 59% still had hypoglycemia requiring medical treatments (resolved by 5 years)
• Hyperglycaemia in 53% immediately after surgery & 100% by 13 years of age
• The cumulative incidence of insulin-treated patients was 42% at 8 years & 91% at 14 years of age

Long term Medical Treatment

• Review of case series/reports on 619 CHI patients (till 2013)

Diazoxide (84%)

• Mean dose of diazoxide: 12.5 (±4.3) mg/kg/day (range 2–60)
• Mean duration of treatment until remission: 5 years
• Side effects of diazoxide were usually not severe

Long term Medical Treatment

**Somatostatin analogues (16%)**

- Mean dose of octreotide $14.9 \pm 7.5$ μg/kg/d (range 2.3–50)
- Lanreotide $67.3 \pm 39.8$ mg/month (range 10–120)
- Mean duration of treatment until remission: 4 years
- Frequent side effects: tachyphylaxis and mild GI symptoms
- The risk of persistent growth deceleration was low (<5 %)

**Others:** Glucagon, Ca channel blockers, high calorie diet

Newer/Futuristic Therapeutic options

• Long acting somatostatin analogues
• mTOR inhibitors
• GLP1 receptor antagonists
• Long-acting soluble glucagon
• Specific somatostatin receptor agonists
• Insulin receptor antibody
Long acting Somatostatin Analogues

- Selective binding affinity for SSTR 2 and 5
- Unlicensed for CHI

**Somatuline autogel (Lanreotide)**
- 30,60,90mg prefilled syringe
- Rapid-release phase, followed by a long-lasting phase of slow release

**Sandostatin LAR (octreotide)**
- 10,20,30mg vials
- Slow release during the first 2 weeks and then increases quickly to reach a stable phase between 3 and 4 weeks
Long acting Somatostatin Analogues

- For patients who do not respond or tolerate diazoxide after a trial of s/c Octreotide

**Starting dosage**

- **Lanreotide** 30–60 mg deep subcutaneous every 4 weeks
- **Sandostatin-LAR** 10 mg intramuscularly every 4 weeks
Benefits

• Better quality of life
• No more daily injections
• Less trauma and pain
• More freedom for child and parents
• Easier to travel – car journeys, flying, holidays
• Cost effective
Side-effects

- Allergic type reactions / local reactions
- GI side effects - anorexia, nausea, abdominal pain, bloating, flatulence, loose stools
- Decrease gallbladder contractility - cholestasis, hepatic dysfunction and gall stones
- Suppression of growth and thyroid hormones (rare)
- Risk of NEC in neonates
- Tachyphylaxis
Monitoring

- Regular blood glucose monitoring and/or CGMS
- Liver function every 4–6 weeks
- Abdominal ultrasound every 3–6 months
- If (asymptomatic) cholelithiasis is present, ursodeoxycholic acid (UDCA) could be tried
- Growth and thyroid function at least 6-monthly
Studies...


Evidence..

- **27** patients (2 focal) in 6 centres [retrospective]
- Beneficial in **89%** [not all had CGMS]
- **48%** some side effects (mainly raised liver enzymes)
- **11%** discontinued due to side effects (local abscess, raised ALT)
- Starting age **2m-17 years**
- Duration of treatment **1-72 months** (average 18 months)
- Dose **5mg-90mg**/month
- Majority on combined therapy with enriched feeds/Diazoxide

mTOR inhibitors

- Used in insulinoma in adults and paediatric post-transplant
- Noted to be beneficial in some severe diffuse CHI patients unresponsive to diazoxide/octreotide
- **Sirolimus** (oral): starting dose 0.5mg/m²/day (max 3mg/m²/day), aim serum level 5-15ng/ml
- Immunosuppressive - close monitoring of serum levels, blood counts, oral cavity, renal and liver function & lipids


Extreme caution on the use of sirolimus for the congenital hyperinsulinism in infancy patient. Banerjee I, De Leon D, Dunne MJ. Orphanet J Rare Dis. 2017 Apr 14;12(1):70

GLP-1

- Glucagon-like peptide-1: produced in L-cells of the intestine in response to meal

- **Stimulates insulin secretion** & inhibits glucagon secretion

- Also inhibits hepatic glucose production, gastric emptying, and appetite
Exendin (9-39)

- Specific GLP-1 receptor antagonist
- Normalizes fasting hypoglycemia in SUR-1(-/-) mice by reducing insulin secretion
- Randomized, open-label, crossover study: 9 K(ATP)HI patients received either exendin-(9-39) or vehicle on two different days; mean nadir blood glucose and glucose AUC were significantly increased by exendin-(9-39)
- Exendin-(9-39) significantly inhibited amino acid-stimulated insulin secretion in pancreatic islets from neonates with K(ATP)HI

Mean fasting blood glucose ± SEM during vehicle and exendin-(9-39)

Pasireotide

- Newer somatostatin analogue – more specific binding to SSTR5
- Inhibition of insulin secretion: SSTR2 and SSTR5
- Inhibition of glucagon secretion: SSTR2
- Octreotide inhibits both insulin and glucagon secretion but Pasireotide suppresses predominantly only insulin
- Used in adults for Cushing’s disease and PPHH – not currently used in children for any medical indication
- Small pilot study to assess the effect of s/c Pasireotide on preventing hypoglycemia due to hyperinsulinism was proposed in >18 years (study withdrawn...as per Clinical Trials website)
CRN02481 (Crinetics Pharmaceuticals)

- New class of **oral selective nonpeptide somatostatin [SST5] agonist**
- Inhibits insulin secretion while avoiding glucagon suppression
- In rats treated with CRN02481 - blood glucose normalised and at higher doses, hyperglycaemia was noted
- Optimizing the good manufacturing process [GMP], synthesis and performing good laboratory practice [GLP]
- Planned for initiating **Phase 1** human proof-of-concept clinical trial that evaluates inhibition of insulin secretion and its effects on blood glucose in **2019**
RZ358 (Rezolute)

• **Intravenous human monoclonal antibody** - counteracts the effects of hyperinsulinemia via allosteric modulation of INSR
  
  • Reverses hypoglycemia in hyperinsulinemic mice and rats
  
  • Increases PP glucose and induces insulin resistance in adults
  
  • Single dose **IV XOMA 358** in CHI patients >12 years – increased fasting and postprandial glucose [hypo reduced by nearly 50%]
  
  • Demonstrated proof-of-concept and safety in Phase 2a studies
  
  • **RZ358** has received designated orphan status in the US & EU
  
  • Rezolute plans to advance clinical development
Novel Soluble Glucagon(s)

- Glucagon - useful in acute phase to stabilise blood glucose (IV/SC/IM) but not stable in aqueous solutions
- Available as lyophilized powder - once reconstituted - begins to degrade and fibrillate rapidly
- Unstable and unsuitable for use long term use in pumps

Newer Soluble Glucagon Preparations

- Dasiglucagon (Zealand pharma)
- CSI-Glucagon™ (Xeris Pharma)
- AmideBio
Dasiglucagon (Zealand pharma)

• Glucagon analog with improved solubility and stability
• **Single dose:** Phase 2 – in T1DM with hypo-achieved glucose increases of >20 mg/dL within a median time of 9-10 mins – safe and tolerated – Phase 3 underway

• **Multi-dose:** Phase 2a studies – in dual-hormone artificial pancreas system in T1DM (with Beta Bionics) – effective, safe and well tolerated; Phase 2b (longer duration) planned

• Received a positive opinion on orphan medicinal product application in US and EU
CSI-Glucagon™ [Xeris Pharma]

- Stable Non-Aqueous Glucagon for Severe Hypoglycemia
- Effective and safe in adults with experimental hypoglycemia
- Phase 3 studies to be undertaken for developing the ready-to-use glucagon auto-injector for hypoglycemia
- **S/c infusion using Omnipod pump** for 48hrs – recruiting for Phase 2 (proof of concept) multi-center, randomized, placebo-controlled, double-blind trial - to assess the efficacy in children < 1 year of age with CHI
- Expected completion Jan 2019
Conclusions

• **Diazoxide** – first line of therapy

Diazoxide unresponsive: rapid genetic testing

• **Focal** – DOPA PET CT, Surgery

• **Diffuse** – medical (octreotide, novel therapies) or surgery

• **Newer/Futuristic medical options...**
Thank You

Alder Hey Children's Hospital, Liverpool, UK